Obvious-Type Double Patenting

Claims 6, 7, 11, and 17-21 stand rejected for obviousness-type double patenting over claims 1 and 2 of U.S. Patent No. 5,712,370. Applicants note that the Office now reasserts this rejection after inadvertently withdrawing it. Applicants request that this rejection be held in abeyance until allowable subject matter has been indicated.

Rejections Under 35 U.S.C. § 102(b)

Claims 17-19 stand rejected as allegedly anticipated by Sytkowski et al. (*J. Biol. Chem.*, 262:1161-65 (1987); "Sytkowski"). Specifically, the Office asserts that (1) claim 17 is drawn to an anti-EPO antibody directed against epitopes that bind to the EPO receptor; (2) claim 18 is drawn to an antibody which neutralizes EPO biological activity; and (3) claim 19 is drawn to a monoclonal antibody . According to the Office, Sytkowski recites two antibodies, anti-peptide 99-118 and anti-peptide 11-129, that are neutralizing antibodies that bind to the receptor binding domain of EPO. Applicants note that this rejection is very similar to the Office's previous rejection of claims 17 and 18 as set forth item 8 in the Office Action of April 27, 2001. In the current Office Action, the Office has not provided any reasons as to why Applicants' arguments were not convincing. Nonetheless, Applicants respectfully traverse the Office's current rejection for the following reasons.

First, as discussed in Applicants' previous response, Sytkowski clearly showed that peptides 99-118 and 111-129 do not directly bind the EPO receptor. Specifically, Sytkowski reported that the six peptides, used to generate their antibodies, failed to demonstrate any EPO biological activity and that these peptides failed to inhibit the biological activity of whole EPO.

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These six peptides included 99-118 and 111-129. More importantly, these authors directly state that "none of these peptides react[s] directly with the erythropoietin receptor" (p.1162, right column, first full paragraph). This is why Sytkowski considers alternative mechanisms by which antibodies to these peptides may be working. *See* page 1165 last paragraph.

Second, Applicants note that the Office has also cited the last paragraph of page 1165 to support its contention that these two antibodies bind to the receptor binding domain of EPO. Applicants respectfully contend that the Office has misconstrued the teaching of this paragraph. On page 1165, Sytkowski discusses two other possible alternative explanations for how neutralizing antibodies may work. In one instance, these antibodies may inhibit EPO activity not by binding the receptor epitopes on EPO, but by binding other sites on the protein that cause an allosteric change in the protein such that the conformation of the EPO receptor binding domain has changed and no longer interacts with the EPO receptor. The second possibility Sytkowski considers is that the anti-peptide 99-118 and anti-peptide 111-129 antibodies may bind the receptor binding domain of the hormone. However, Sytkowski presented conflicting data showing that these peptides in fact do not bind the EPO receptor, which is why Sytkowski calls for further experimentation to determine how these antibodies work. Applicants submit that there is a third possible mechanism by which a neutralizing antibody may function that Sytkowski does not consider. Specifically, such an antibody could bind near the EPO receptor binding domain, thereby physically blocking the interaction of EPO with its receptor. Thus, Sytkowski's disclosure offers no proof that the anti-peptide 99-118 and anti-peptide 111-129 antibodies bind to a portion of EPO that binds to the EPO receptor. For these reasons, Sytkowski

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cannot anticipate claims 17-19. Applicants therefore respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 102(b).

Claims 5, 6, 11, 12, 17, 20, and 23 stand rejected under § 102(b) as allegedly anticipated by Lin (U.S. Patent 4,703, 008; "Lin"). The Office asserts that claim 5 is drawn in part to a method of using an EPO peptide for preparation of an antibody, wherein the EPO peptide consists essentially of a peptide of less than the complete EPO protein, the peptide selected from the group consisting of amino acids 152 to 166 (P2/1). Claim 6 allegedly recites an antibody directed against the EPO peptide wherein the EPO peptide consists essentially of a peptide of less than the complete EPO protein, the peptide selected from the group consisting of amino acids 152 to 166 (P2/1). The Office notes that Lin discloses polyclonal antibodies produced by immunization with a peptide spanning amino acids 144-166, which, according to the Office, produces neutralizing antibodies that bind EPO. Applicants respectfully traverse the Office's rejection on the following grounds.

First, Lin's peptides do not overlap in scope with the claimed peptides. As discussed in Applicants' previous response, the term "consisting essentially of" may include the claimed P2/1 peptide with a small number of amino acids added to it such that the new peptide generates the antibodies of the invention. As Lin's peptide spans amino acids 144-166, 8 amino acids have been added to the amino terminal end of the P2/1 peptide, which is only 15 amino acids long. This addition represents a 50% increase in size of the peptide. The addition of this many amino acids may affect the ability of the resulting peptide to elicit the antibodies of the invention, thus falling outside the scope of the claimed invention.

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Second, regarding the Office's rejection of independent claim 6, Applicants note that Lin does not disclose all of the elements of this claim. Specifically, contrary to the Office's summary of Lin, this reference does not demonstrate that the disclosed antibodies neutralize the biological activity of EPO. The invention of independent claim 6 recites "wherein said antibody neutralizes the biological activity of EPO . . . ." Because Lin does not disclose information on neutralization of EPO, Lin lacks all of the elements of claim 6 and thus cannot anticipate the claim.

Finally, though Lin's antibodies immunoprecipitate intact EPO, this does not necessarily demonstrate binding specifically to the domain of EPO that interacts with the EPO receptor, as required by independent claim 17. Moreover, Lin provides no direct evidence that the antibodies generated to the disclosed peptides (col. 36) bind this EPO domain. Furthermore, Lin states that "[p]reliminary *in vivo* activity studies on the three peptides revealed no significant activity either alone or in combination" (col. 36, lines 34-36) which further undermines the notion that the antibodies generated by Lin bind to a region of EPO that interacts with the EPO receptor.

For the reasons set forth above, Lin fails to disclose all of the elements of independent claims 5, 6, and 17. Thus, Lin cannot anticipate these claims or dependent claims 11, 12, 20, and 23. Applicants therefore respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 102(b).

Rejection Under 35 U.S.C. § 103(a)

Claim 10 stands rejected under § 103(a) as allegedly upatentable over Sytkowski in view of Yanagawa et al. (*Blood*, 64:357-64 (1984); "Yanagawa"). The Office asserts that claim 10 is directed to a method of using the antibody of claim 6 for purifying EPO. According to the

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Office, Sytkowski teaches the antibody of claim 6 because this reference discloses neutralizing antibodies to two EPO peptides, 99-118 and 111-129. Yanagawa allegedly teaches a method of purifying human EPO using monoclonal antibodies to EPO. The Office thus contends that it would have be obvious to one of ordinary skill to combine Sytkowski's antibodies with Yanagawa's method of purification. Applicants traverse the Office's rejection on several grounds.

First, Sytkowski does not teach the antibody of claim 6. Specifically, Sytkowski does use peptides 99-118 and 111-129 to generate neutralizing antibodies. But, claim 6 recites neutralizing antibodies directed to an EPO peptide that "consists essentially of a peptide less than the complete erythropoietin protein, said peptide having an amino acid sequence selected from the group consisting of amino-acid positions 138-166 . . . and 152-166. . . ." Sytkowski's peptides do not overlap the peptides of claim 6. Thus, the antibodies generated in Sytkowski cannot possibly be the antibodies of claim 6, as the immunogens are completely different. Thus, Sytkowski does not teach the antibody of claim 6.

Second, Applicants respectfully contends that the Office has misunderstood the teaching of Yanagawa. The Office asserts that Yanagawa teaches a method of purifying EPO using monoclonal antibodies to EPO. Yanagawa did not use anti-EPO monoclonal antibodies ("MAbs") to purify EPO. The goal in Yanagawa was to purify EPO well enough to obtain an EPO preparation that could be used to generate anti-EPO antibodies. To this end, Yanagawa used two columns containing antibodies directed to contaminants present in their partially purified EPO sample to remove those contaminants before attempting to further purify EPO

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itself. *See* page 360, right column. Yanagawa did this because the initial attempt to generate EPO specific MAbs from partially purified EPO failed. These two anti-contaminant MAb columns did not remove all the contaminants, which is why Yanagawa continued to purify EPO via SDS-PAGE. Yanagawa then used the resulting SDS-PAGE purified EPO to produce MAbs directed to EPO. Thus, Yanagawa does not teach a method of purifying EPO using anti-EPO MAbs. Rather, Yanagawa used MAbs directed to contaminants present in their partially purified EPO preparation to remove most of these contaminants followed by SDS-PAGE purification. Yanagawa notes that "[t]he most effective procedure in purification of Ep appears to be removal of contaminants with immunoadsorbent columns. . .," teaching away from the claimed concept of using anti-EPO antibodies to purify EPO.

In sum, neither Sytkowski nor Yanagawa alone or in combination make the invention of claim 10 obvious. Specifically, Sytkowski does not teach the antibody of claim 6 and Yanagawa does not teach purification of EPO using anti-EPO antibodies. Applicants therefore respectfully request reconsideration and withdrawal of the Office's rejection of claim 10 under 35 U.S.C. § 103(a).

Conclusion

Applicants respectfully request that this Response be entered by the Office, placing claims 5-7, 9-12, and 14-23 in condition for allowance.

In view of the foregoing remarks, Applicants submit that their claimed invention is not anticipated in view of the prior art reference cited against this application. Applicants therefore

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respectfully request the entry of this Response, the Office's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Please grant any additional extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: December 21, 2001

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